IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No. : Axel ULLRICH et al
Applicant : 10/563,211
Filed : January 4, 2006
TC/A.U. : 1614
Examiner :

Docket No. : 2923-743
Customer No.: 6449
Confirmation No.: 6030

SUBMISSION OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Submitted herewith is a copy of the translation of the International Preliminary Examination Report.

In the event that any fees are due with this paper, please charge our Deposit Account No. 02-2135.

Respectfully submitted,

By _____
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RBM/cb

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING TRANSMITTAL OF COPY OF INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (CHAPTER I OF THE PATENT COOPERATION TREATY)
(PCT Rule 44bis.1(c))

To:

WEISS, Wolfgang
Weickmann & Weickmann
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81635 München
ALLEMAGNE

Date of mailing *(day/month/year)* 19 January 2006 (19.01.2006)	
Applicant's or agent's file reference 31063P WO	**IMPORTANT NOTICE**
International application No. PCT/EP2004/007329	International filing date *(day/month/year)* 05 July 2004 (05.07.2004)
Priority date *(day/month/year)* 04 July 2003 (04.07.2003)	
Applicant MAX-PLANCK-GESELLSCHAFT ZUR FÖRDERUNG DER WISSENSCHAFTEN E.V. et al	

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.+41 22 740 14 35	Authorized officer Ellen Moyse Facsimile No.+41 22 338 89 75

Form PCT/IB/326 (January 2004)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 31063P WO	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/EP2004/007329	International filing date *(day/month/year)* 05 July 2004 (05.07.2004)	Priority date *(day/month/year)* 04 July 2003 (04.07.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant MAX-PLANCK-GESELLSCHAFT ZUR FÖRDERUNG DER WISSENSCHAFTEN E.V.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

   - ☒ Box No. I — Basis of the report
   - ☐ Box No. II — Priority
   - ☒ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV — Lack of unity of invention
   - ☒ Box No. V — Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI — Certain documents cited
   - ☐ Box No. VII — Certain defects in the international application
   - ☒ Box No. VIII — Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 09 January 2006 (09.01.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 740 14 35	Authorized officer Ellen Moyse Telephone No. +41 22 338 89 75

IPC OK

PATENT COOPERATION TREATY

REC'D 16 DEC 2004
WIPO PCT

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

20/1

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)
	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/007329	05.07.2004	04.07.2003

International Patent Classification (IPC) or both national classification and IPC
A61K38/00, A61K48/00, A61K39/395

Applicant
MAX-PLANCK-GESELLSCHAFT ZUR FÖRDERUNG DER ...

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/007329

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-30 (all partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-30 (all partially) are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☒ the claims, or said claims Nos. 1-30 (all partially) are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-30 (all partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/007329

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9,30
	No:	Claims	10-29
Inventive step (IS)	Yes:	Claims	1-9 30
	No:	Claims	10-29
Industrial applicability (IA)	Yes:	Claims	1-29
	No:	Claims	-

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Present claims 1,10-12,28 and 30 relate to inhibitors of an extremely large number of possible receptor tyrosine kinase ligands. In fact, the claims contain so many options, that a lack of clarity (and conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.
Further, support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the inhibitors of receptor tyrosine kinase ligands claimed. In the present case, the claims contain so many options, that a lack of clarity (and conciseness) within the meaning of Article 6 PCT arises and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Consequently, the search has been carried out for those parts of the application which do appear to be clear and supported, namely for those parts relating to the inhibitors of those receptor tyrosine kinase ligands, which are specifically mentioned in claim 19 and in the description (page 6, lines 8-14 and lines 28-31 first half).
Hence, it is pointed out, that the present Written Opinion only relates to the searched subject-matter of the above mentioned claims.

2. For the assessment of the present claim 30 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claim. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: FR2828104 (CT HOSPITALIER UNIVERSITAIRE D E MONTPELLIER) 07-02-2003& WO03013485 (CT HOSPITALIER UNIVERSITAIRE D E MONTPELLIER) 20-02-2003
D2: WO9832748 (HOFFMANN LA ROCHE ; AGOURON PHARMA (US)) 30-07-1998
D3: WO9416738 (HEKTOEN INST FOR MEDICAL RESEARCH) 04-08-1994
D4: WO03051825 (EXELIXIS INC.) 26-06-2003
D5: WO0166557 (HUMAN GENOME SCIENCES INC.) 13-09-2001

1. **Novelty and inventive step (Art. 33(2)(3), PCT)**

1.1 It should be noted that the document indicated in the search report as "PX"-document has not been taken into consideration for the evaluation of novelty and inventive step, because the priority of the present application has been **assumed** to be valid (see also official Journal EPO, 11/2001, page 539-542, especially item 13).

1.2 It is pointed out that the present opinion concerning novelty, inventive step and industrial applicability only refers to subject-matter for which an International Search Report has been established (see item III).

1.3 The application relates to the use of an inhibitor of a receptor tyrosin kinase (RTK) ligand, preferably HB-EGF, for the manufacture of a medicament for
- treating a hyperproliferative disorder, which is at least partially therapy-resistant,
- treating a hyperproliferative disorder, which is caused by a stress-induced activation of an RTK,
- increasing the efficiency of therapies against such disorders,
- increasing the sensitivity of such disorders against irradiation and/or medical treatment,

as well as to a pharmaceutical compositions comprising such inhibitor in combination with a further medicament.

The inhibitor can be e.g. an antibody directed against an RTK ligand, an inhibitor acting on the nucleic acid or protein level or a low-molecular weight inhibitor. Further, the inhibitor can be a direct RTK ligand inhibitor, or an inhibitor of a metalloprotease which is capable of cleaving the RTK ligand.

1.4 D1 discloses the use of HB-EGF inhibitors, e.g. heparin, diphtheria toxine, anti-HB-EGF antibodies, for use against hyperproliferative diseases (page 1, lines 1-16; page 2, lines 9-29; page 3, lines 17-23; Example 10). Further the use of a combination of HB-EGF inhibitors and IL-6 inhibitors (e.g. corticoides or monoclonal anti-IL-6 antibodies) is claimed.
Therefore, subject-matter of claims 10-20,22,26,27 lacks novelty in view of D1 and subject-matter of claims 23-25 lacks inventive step, since it is generally known to the skilled person that the features of claims 23-25, namely inhibitors, which act on the nucleic acid level, are equivalent in their effect to direct RTK ligand inhibitors and can be interchanged where circumstances make it desirable.

1.5 D2 claims sulfonamide compounds, which have an inhibitory effect on TNF as well as on matrix metalloprotease (MMP), and their use for manufacturing a medicament for treating hyperproliferative disorders. It is also mentioned that MMP inhibitors inhibit the release of biologically active molecules from cells, like TGF-α, EGF, HB-EGF and thus have a beneficial effect on diseases like cancer (page 1, lines 23; page 3, lines 20-32; claims 78-80).
In view of D2, subject-matter of claims 12-16,18-22,26-29 cannot be regarded as novel and no inventive step can be acknowledged for subject-matter of claims 23-25, since the skilled person would regard it as a normal design option to use a specific inhibitor which acts on the nucleic acid level instead of a direct inhibitor.

1.6 D3 discloses the use of TGF-α antisense RNA, preferably in combination with EGFR antisense RNA and an EGFR antibody for the manufacture of a medicament for treating hyperproliferative diseases (especially prostate cancer) and compositions comprising such TGF-α inhibitors (page 23, line 19-page 25, line 8; page 28, line 9-page 31, line 28).
Subject-matter of claims 10-16,18,19 and 22-25 is anticipated by D3 and subject-matter of claims 26 and 27 lacks inventive step, since it is generally known to the skilled person that a specific inhibitor which acts on the nucleic acid level can be exchanged for a direct inhibitor to achieve a given effect.

1.7 D4 discloses the use of ADAM-10 inhibiting compounds for the manufacture of a medicament against hyperproliferative diseases and claims pharmaceutical compositions comprising such inhibitors alone or in combination with other anti-cancer agents (paragraphs [0009] and [0063]).

1.8 D5 claims *inter alia* the use of antagonists to ADAM proteins, like e.g. antibodies or small molecules, for the manufacture of a medicament against hyperproliferative diseases and conditions associated with stress. The combination of such antagonists with other medicaments or chemotherapy or radiation therapy is also suggested (paragraphs [0175]-[0179],[0191],[233],[327], [407],[449],[478],[502]-[504]).

In view of D4 and D5, subject-matter of claims 10-19,21,22 and 26-29 lacks novelty and subject-matter of claims 23-25 does not seem to involve an inventive step.

1.9 It is pointed out that the discovery of a novel mechanism cannot confer novelty to second medical use claims, which refer to a known medical use, as is presently claimed in claim 12.

Re Item VIII
Certain observations on the international application

2. Clarity of the claims (Art. 6, PCT)

2.1 It appears from the description (page 5, line 18-21) that new claim 11 should refer to the use of an "inhibitor of a receptor tyrosine kinase **ligand**" instead of the use of an "inhibitor of a receptor tyrosine kinase".

2.2 Similarly, claim 18 should refer to the "**use** of any one of claims 1-17..." instead to "method of any one of claims 1-17..."

2.3 Further, claim 22 seems to refer to claims "1-21" instead of "1-12".